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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/297,668	05/06/99	GERSHONI J	27/135

HM12/0412

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EXAMINER	
FORMAN, B	
ART UNIT	**PAPER NUMBER**
1655	9

DATE MAILED: 04/12/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/297,668	GERSHONI ET AL.	
	Examiner	Art Unit	
	BJ Forman	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *112-143* is/are pending in the application.

4a) Of the above claim(s) *112-136* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *137-143* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s) _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. This action is in response to papers filed 15 February 2001 in Paper No. 8 in which claims 134-140 were amended. All of the amendments have been thoroughly reviewed and entered. The previous rejections in the Office Action of Paper No. 7 dated 6 December 2000 under 35 U.S.C. 112, second paragraph are withdrawn in view of the amendments. The previous rejection of Claims 137-143 under 35 U.S.C. 103(a) is maintained. All of the arguments have been thoroughly reviewed and are discussed below.

Currently claims 137-143 are under prosecution.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 137-143 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gritz et al. (U.S. Patent No. 5,691,170, issued 25 November 1997) in view of Mandeville et al. (U.S. Patent No. 6,031,071, filed 24 January 1996).

Regarding Claim 137, Gritz et al. teach a method for preparing a peptide of a discontinuous epitope (Column 9, lines 54-57) of a single biological unit of an organism wherein the single biological unit is the HIV env gene (Example 3) the method comprising the steps of: providing a plurality of DNA fragments corresponding to at least a portion of a genome by digesting said at least a portion of said genome of the organism to form said plurality of fragments; ligating said plurality of fragments to form at least one ligated fragment i.e. plasmid

pAbT4075 with the HIV-1 BH10 env gene and plasmids pAbT4082 with the HIV-1 RF env gene (Example 3, Column 13, lines 35-46); at least partially digesting said at least one ligated fragments to form a plurality of fragments coding for the discontinuous epitope of the single biological unit i.e. plasmid pAb4085 with HIV-1 BH10 env gene and the HIV-1 RF env gene (Column 13, lines 59-62 and Fig. 6); inserting said discontinuous epitope into an expression system i.e. viral genome (Example 4, Column 13, lines 65-67 and Fig. 7) and they further teach obtaining a peptide from said expression system wherein the presence of the obtained peptide is confirmed by anti-HIV antibody recognition (Example 7, Table 1). Gritz et al. teach the method wherein said plurality of fragments coding for the discontinuous epitope are inserted into the vial genome wherein following a recombination event a discontinuous epitope is formed and wherein number of different recombination events occur to thereby form a discontinuous library i.e. a diverse set of chimeric env genes (Example 4, Column 14, lines 17-20) but they do not teach forming said discontinuous library prior to inserting said library in to said expression system. Mandeville et al. teach a similar method for preparing a conformational peptide of a discontinuous epitope i.e. "peptides that represent discontinuous amino acids" (Column 7, lines 33-37) the method comprising: providing a plurality of DNA fragments corresponding to at least a portion of a genome of an organism, ligating said plurality of fragments to form at least one ligated fragment thereby forming a discontinuous library; inserting said library into an expression system wherein each discontinuous epitope of the library is inserted 5' of a sequence encoding a coat protein and obtaining the peptide from said expression system (Column 6, lines 42-58). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the insertion followed by recombination to form the discontinuous library of Gritz et al. with the direct insertion of the discontinuous epitopes 5' to a coat protein whereby expressed epitopes are displayed as a portion of an outer structural protein of the bacteriophage for the expected benefit of screening the displayed discontinuous epitopes to identify the best diversity of epitopes binding to any

ligand and using the displayed discontinuous epitopes as an immunogen to produce antibodies as taught by Mandeville et al. (Column 4, lines 20-30).

Regarding Claim 138, Gritz et al. teach the method wherein said expression system comprise a plurality of bacteria (Column 14, lines 27-38) but they do not teach step (d) is performed by inserting each of said plurality of fragments of said discontinuous library into genetic material of said bacteria. Mandeville et al. teach a similar method for preparing a conformational peptide wherein step (d) is performed by inserting each of said plurality of fragments of said discontinuous library in to genetic material of said bacteria i.e. bacterial host cells are transformed with a bacteriophage expression vectors comprising the discontinuous library (Column 7, lines 14-21). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the bacterial expression system of Gritz et al. with the bacteriophage expression system for their known benefits as a powerful tool for the selection of peptide sequences as taught by Mandeville et al. (Column 2, lines 48-53).

Regarding Claim 139, Gritz et al. teach the method wherein said expression system comprises a plurality of viral vectors and step (d) is performed by inserting each of said plurality of fragments of said discontinuous library into genetic material of each of said viral vectors (Column 13, lines 65-67) but they do not teach the viral vectors are phages. Mandeville et al. teach the similar method wherein said expression system comprises a plurality of viral vectors which are phages and step (d) is performed by inserting each of said plurality of fragments of said discontinuous library into genetic material of each of said phage (Column 7, lines 14-21). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the bacterial expression system of Gritz et al. with the bacteriophage expression system for their known benefits as a powerful tool for the selection of peptide sequences as taught by Mandeville et al. (Column 2, lines 48-53).

Regarding Claim 140, Gritz et al. al. teach the method wherein each of said plurality of fragments is a portion of the HIV env gene (Example 3, Column 13), but they do not teach the fragments are cloned in to a phage gene coding for a coat protein. Mandeville et al. teach the similar method wherein each of said plurality of fragments is cloned in to a phage gene coding for a coat protein such that the peptide is displayed by said coat protein (Column 6, lines 42-49). It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the bacterial expression system of Gritz et al. with the bacteriophage system of Mandeville et al. wherein the expressed fragments are displayed for the known benefits of phage display i.e. powerful selection tool for identifying peptides which bind to pre-selected targets, for identifying target analogs and for antibody production (Column 6, lines 19-41).

Regarding Claim 141, Mandeville et al. teach the method where in said plurality of phages are filamentous phages and said coat protein is pIII (Column 4, lines 33-36). It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the bacterial expression system of Gritz et al. with the bacteriophage system of Mandeville et al. wherein the expressed fragments are displayed for the known benefits of phage display i.e. powerful selection tool for identifying peptides which bind to pre-selected targets, for identifying target analogs and for antibody production (Column 6, lines 19-41).

Regarding Claim 142, Gritz et al. teach a conformational peptide of a single biological unit of an organism i.e. HIV env gene (Example 7, Column 16) wherein the peptide is produced by expressing a discontinuous epitope library and wherein the production of the peptide is confirmed by anti-HIV env antibody recognition (Column 16, Table 1) but they do not teach producing the peptide by forming a discontinuous library prior to inserting said library into said expression system. Mandeville et al. teach the similar method for preparing a conformational peptide of a discontinuous epitope (Column 7, lines 33-37) wherein each

discontinuous epitope of the library is inserted 5' of a sequence encoding a coat protein and obtaining the peptide from said expression system (Column 6, lines 42-58). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the insertion followed by recombination to form the discontinuous library of Gritz et al. with the direct insertion of the discontinuous epitopes 5' to a coat protein whereby expressed epitopes are displayed as a portion of an outer structural protein of the bacteriophage for the expected benefit of screening the displayed discontinuous epitopes to identify the best diversity of epitopes binding to any ligand and using the displayed discontinuous epitopes as an immunogen to produce antibodies as taught by Mandeville et al. (Column 4, lines 20-30).

Regarding Claim 143, Gritz et al. teach a method for vaccinating a subject i.e. a rabbit, against an organism i.e. HIV (Column 9, lines 36-39) comprising the steps of: preparing a conformational peptide of a single biological unit of the organism according to the method of Claim 137 (Example 3, Column 13); placing said peptide in a vaccine carrier i.e. poxvirus (Column 9, lines 44-49); administering said conformational peptide in said vaccine carrier to the subject (Example 7, Column 16) but they do not teach producing the peptide by forming a discontinuous library prior to inserting said library into said expression system. Mandeville et al. teach the similar method for preparing a conformational peptide of a discontinuous epitope (Column 7, lines 33-37) wherein each discontinuous epitope of the library is inserted 5' of a sequence encoding a coat protein and obtaining the peptide from said expression system (Column 6, lines 42-58). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the peptide production by random recombination of Gritz et al. with specific production of the peptide within a coat protein for the expected benefit of using the produced peptide "as is" as an antigen in a vaccine composition as taught by Mandeville et al. (Column 2, lines 51-52).

Response to Arguments

4. Applicant argues that Gritz et al. do not teach the claimed invention because they teach a combination of DNA fragments derived from two different yet homologous genes while the instant application claims are drawn to a peptide which represents an epitope which is discontinuous in its primary amino acid sequence of a single biological unit of an organism. The argument is not found persuasive because Gritz et al. teach an epitope which is discontinuous in its primary amino acid sequence of a single biological unit (i.e. env gene) of an organism (i.e. HIV). Additionally, the argument is not found persuasive because the chimeric polypeptide encoding the HIV env antigen of Gritz et al. encompasses the biological unit as defined by the specification i.e. "preferably" a polypeptide (page 13, line 1).

Applicant further argues that Grits et al. does not suggest recombination of non-homologous sequences within a single sequence. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., recombination of non-homologous sequences within a single sequence) is not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant argues that Mandeville et al. merely teach random peptide libraries and do not teach or suggest the claimed invention which provides for analysis of biological units too complex to be analyzed using the random peptide approach of Mandeville et al. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the above rejection is based on the teaching of Gritz et al. combined with the Mandeville et al. and the Mandeville reference is merely cited for its teaching of standard methodology which is routinely practiced in the art i.e. phage display library.

Additionally, applicant argues Mandeville et al. do not teach or suggest that discontinuous amino acid binding sites may be generated in a non-random approach and therefore the instant invention is not obvious over the teaching of Gritz et al. in view of Mandeville et al. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837

F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Gritz et al. teach a method for preparing a peptide which is discontinuous in its primary amino acid sequence and Mandeville et al. teach phage display library. The courts have stated that the order of steps for performing a method is *prima facie* obvious in the absence of new or unexpected results (*In re Burhans*, 154 F2d 690, 69 USPQ 330). Therefore, it would have been *prima facie* obvious to one of skill in the art to change the order of the method steps in the method of Gritz et al. to obtain the claimed invention and to apply the library teaching of Mandeville et al. to the peptide preparation of Grit et al. for the known benefits of powerful peptide selection as taught by Mandeville et al. (Column 2, lines 48-53).

Conclusion

5. No claim is allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:45 TO 4:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.
April 11, 2001